OXIDATION OF AROMATIC ACID HYDRAZIDES BY THALLIUM(III) IN ACIDIC MEDIUM - A KINETIC AND MECHANISTIC APPROACH

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BY

Mr. SAMADHAN H. NIKALAJE
M.Sc. NET.

UNDER THE GUIDANCE OF

Dr. AMIT S. VARALE
M.Sc., Ph.D.
DEPARTMENT OF CHEMISTRY

A.S.P. COLLEGE DEVRUKH

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Title of the topic	:	"Oxidation of Aromatic Acid Hydrazides by Thallium(III) in Acidic Medium - A Kinetic and Mechanistic Approach"
Name of the Students	:	Mr. Samadhan Hanumant Nikalaje
Basic Qualification	:	M.Sc.(Organic Chemistry), NET
In the case of Ph.D. student Year of Passing of PET/NET/SET/M.Phil/GPAT /GATE (Teaching Experience)	:	NET-LS 9 Years, 10 Months
Name of the Research Supervisor/Guide	:	Dr. Amit Shrikant Varale Assistant Professor in Chemistry
Date of Superannuation/Retirement of the Research Supervisor/Guide	:	30 November 2039.
Name of the Research Centre	:	A.S.P.College Devrukh, Dist.-Ratnagiri
Signature of the Student	:	
Signature of the Research Supervisor/Guide	:	

Date: 04/10/2021

Signature of Head/Director/Principal/Research Centre

Seal of College/Department

NYA. ATHALYE, VED. SAPRE, VID. PITRE COLLEGE DEVRUKH

PRINCIPAL,
VIDHIDNYA PITRE SCIENCE COLLEGE
DEVRUKH (DIST. RATNAGIRI) PIN - 415 804

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1. Title

"Oxidation of Aromatic Acid Hydrazides by Thallium (III) in Acidic Medium

- A Kinetic and Mechanistic Approach"

2. Aims of the study

The aim of the study is to determine rate of reaction under various reaction conditions. The substituted substrates used for this are cost-effective, easily available and environment friendly. Our emphasis is to study the effect solvent on the rate of reaction and to determine equilibrium constant. In addition to this we are going to co-relate the rate of reaction with Hammett parameter σ and reaction constant ρ.

3. Objective of the study

Hydrazide derivatives are the type of organic compounds containing a nitrogen-nitrogen covalent bond with one of the substituents being an acyl group. They have gained prominence because of their antibacterial, anti-inflammatory, anticancer, antiplatelet, antimalarial, analgesic and antioxidant activity [1, 2].

The objective of the present study is not only to develop method for the oxidation of hydrazides to their corresponding carboxylic acids but also to determine order of reaction and to propose the plausible mechanism of the reaction. The hydrazides are structurally related and are having different substituents.

Hence, in addition to suggest the reaction pathway, the scope of the present work also includes

i. The examination of the effect of substituents and their positions on reaction rate as well as on mechanism of the reaction.
ii. The determination of Thermodynamic parameters
iii. The determination of Equilibrium constant
iv. Study of effect of solvent
v. Study of Hammett equation

4. Study Background (Literature Review) and significance of study

Chemical kinetics, also known as reaction kinetics, is the study of rates of chemical processes [3]. To study kinetics, oxidation and spectroscopic analysis of aromatic acid hydrazides by using metal oxide have key objective of organic and medicinal chemistry. It is used to synthesize molecule that possesses potent therapeutic value [2]. QSAR has been very useful tool in designing various substituted substrate and reaction progress which is co-related with Hammett parameter [2].Hydrazides are the derivatives of carboxylic acid, ester and hydrazine hydrate [4].

Recently Thallium (III) nitrate trihydrate (TNT) [4] Selenium dioxide [5] Ceric Ammonium Nitrate (IV) [6, 7] Hexamolybdochromate – (III) [8, 9] and sodium per borate [10] have been reported for the oxidation of hydrazide to ester/acid. However most of these methods have several limitations such as oxidizing reagents use are often expensive, toxic, hazards to human being (Non-ecofriendly) and incompatible with the other functional groups present in the substituted substrate.

Recently earliest review study on the oxidation of aromatic acid hydrazides by using Hexacyanoferrate-(III) in aqueous alkali medium [11, 12] required higher concentration of alkali, and it is costly and Non-ecofriendly chemical process. A kinetics and mechanistic study permanganate oxidation fluorenone hydrazine in alkaline medium have been shown viable reaction parameter [13].

The oxidizing agents such as nitric acid, chromic acid, permanganates, ceric sulphate, lead tetra acetate, Thallium, $Ti(CH_3COO)_3$,Cr(VI) Oxide, peroxydisulphate, Mn(II) pyrophoshate, Mn(II) acetate, Mn(III) sulphate, Vanadium, selenium dioxide, hexacyanoferrate(III), aluminiumalkoxide, Osmium tetroxide, pyridine complex, organic peracids, periodic acid, peroxytrifluoroacetic acid, chloramine-T, bromamine-T, N-bromosuccinamide etc., have been widely used to study the oxidation of different organic compounds, Many of these are highly selective in their action on various functional groups.

Thallium (III) salts, which are wellknown oxidants in organic chemistry,have not yet been employed for the oxidation of hydrazides of carbon-nitrogen bonds: 1) Cleavage of oximes and semicarbazones to obtain aldehydes or ketones and 2) the preparation of alkynoic esters or allenic esters from 5-pyrazolanes and their condensed analogs.

The potential of this oxidant is realized more and more as is evident from the considerable amount of work that is lately being done. Thus, the selectivity of thallium (III) is

higher than its neighbors in the periodic table, mercury (II) and lead (IV) and also thallium (III) is a better oxidant than the other two.

Hence we have planned to study kinetics and mechanism of oxidation reaction with Thallium (III) acidic medium.

5. National Status

Hydrazides are the derivatives of hydrazine and carboxylic acids which are used as significant preparatory materials in synthetic organic chemistry [9]. These compounds form complexes with transition metals and make them effective reagents for extraction of metal, polymer stabilization and for ion exchange problems. Hydrazides also have various properties like bactericidal, anti-fungal, carinostatic and also their biological activity increases by complexation with metal ion. The carbonyl oxygen and the nitrogen of the amino group of the hydrazine moiety of the hydrazide form bidentate ligands with the metal ions [14-19]. Most oxidant reacts with hydrazides which produce the corresponding acids and also some oxidant convert them into esters, amides or N-N-diacylhydrazines Polyoxomolybdates of the Keggin structure have been utilized as oxidation catalysts for various catalytic oxidations of organic and inorganic compounds and their mechanism was also proposed [10].

K. K. Gupta and U. Chatterjee reported the oxidation of D-glucose 6 phosphate by hexachloroiridate (IV) and tetrachloroaurate (III) [20] at constant concentration of sugar, acid and temperature. The first order rate constant was found and rate was enhanced by increasing sodium chloride concentration. In spite of these works it has been observed that very less work has been done in acidic medium.

A variety of oxidizing agents have been used for the conversion of hydrazides into the corresponding acids, but with the formation of undesired side products along with the expected esters/acids. Sodium hexanitrocobaltate (III) – catalyzed oxidation of hydrazides leads to the formation of acyl azides rather than esters/acids. Recently thallium (III) nitrates trihydrate (TNT) [4] and ceric (IV) ammonium nitrate [6] (CAN) have been reported for the oxidation of hydrazides to esters / acids.

G.S.Gokavi and J.R.Raju studied the chromium(VI) oxidation of thallium(I) in 60% acetic acid containing 1.25 mol dm^{-3} hydrochloric acid is a second order reaction. The complementary reaction between $Tl^{1}$and $AuCl_4$ was studied in 3.0 mol dm^{-3}HCl medium by Anna N Gidd and Gavisiddapa S Gokavi. The reactive species of oxidant and reactant were found to be $HAuCl_4$ and $TlCl_2^-$, respectively.

Hence, in addition to suggest the reaction pathway, the aim of the present work also includes the examination of the effect of substituents and their positions on reaction rate as well as on mechanism of the reaction.

The literature survey on oxidation of various organic compounds including hydrazides revealed that oxidation of hydrazide appears not to have received much attention.

6. International Level

Isoniazid (pyridine-4-carboxylic acid hydrazide) also known as isonicotinylhydrazide (INH) is used as Antituberculosis - agent. Isoniazid also has an antidepressant effect, and it was one of the first antidepressants discovered. Isoniazid is a prodrug and must be activated by a bacterial catalase-peroxidase enzyme called KatG[1].KatG couples the isonicotinic acyl with NADH to form isonicotinic acyl-NADH complex. This complex binds tightly to the enoyl-acyl carrier protein reductase known as InhA, thereby blocking the natural enoyl-AcpM substrate and the action of fatty acid synthesis. This process inhibits the synthesis of mycolic acid, required for the mycobacterial cell wall. A range of radicals are produced by KatG activation of Isoniazid, including nitric acid [3]. The study of isoniazid has been done by using different techniques like spectroscopy [21], spectrophotometry [22], EPR spectroscopy, HPLC, liquid chromatography, differential pulse polarography, electrochemical, electro analytical etc...

7. Study Hypotheses

A kinetics and mechanistic study of permagnatic oxidation fluorenone hydrazine in alkali medium have been shown viable reaction parameter [13]; therefore it is necessary to get remarkable parameter and appropriate characterization of acid hydrazide will be performed in acidic medium.

Recently Thallium-(III) nitrate trihydrate (TNT) [4] Selenium dioxide [5] Ceric Ammonium Nitrate (IV) [6, 7] Hexamolybdochromate – (III) [8, 9] and sodium per borate [10] have been reported for the oxidation of hydrazide to ester/acid. However most of these methods have several limitations such as oxidizing reagents use are often expensive, toxic, hazards to human being (Non-ecofriendly); therefore it is necessary to perform chemical process in aqueous acidic medium.

Literature review reports kinetics and mechanistic study of aromatic acid hydrazides therefore it is necessary to analyses acid hydrazide by using characterization i.e.^{13}C-NMR,^{1}H-NMR, IR, GC-MS, UV-Visible etc...

8. Study Rationale

Kinetics of study aromatics acid hydrazide expect excellent outcome relate to order of reaction, rate of reaction, equilibrium constant, Hammett parameter and characterization i.e.^{13}C-NMR,^{1}H-NMR, IR, GC-MS, UV-Visible etc.

9. Research Methodology

Thallium solution was prepared by dissolving Tl_2O_3 (ACROS) in 1.0 mol.dm^{-3} HCl and the concentration was ascertained by iodometric titrations .The Aromatic carboxylic acid hydrazides will be prepared from reported procedure and characterized by determining their melting points. Stock solution of aromatic carboxylic acid hydrazides will be prepared in 50 %v/v1, 4 dioxane.

The reaction will be carried out in 50%v/v 1-4 dioxane (spectrochem) under pseudo first order condition keeping concentration of hydrazide in large excess over that of oxidants. The solution containing the reactants and all order constituents were thermally equilibrated separately, mixed and the reaction mixture will be analyzed for unreacted thallium (III) iodometrically by titrating against standard thiosulphate. The pseudo first order rate constant will be determined from the slopes of linear log Tl (III) verses time plots. The result will be reproducible. Kinetics run should followed to about three half-lives of the reactions.

10. Statistical Plan

Months	Plan of Research work
1 to 6	Course work and Literature review
7 to 12	Laboratory work
13 to18	Result analysis and outcome
19 to 30	Synopsis and thesis writing

11. Limitations of the Study

The metal oxide used for the oxidation of aromatic acid hydrazides is economical, so it is used in the dilute form. The outcome obtained will be appealing.

12. Expected Outcomes of Study

Phase - I: kinetics of oxidation of Benzoic and substituted benzoic acid hydrazides by Thallium (III) in acidic medium.

Phase - II: Kinetics of oxidation of Heterocyclic hydrazides by Thallium (III) in acidic medium.

Phase - III: Interpretation of results, characteristics and submission of work to reputed journal for publication.

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Mr. S. H. Nikalaje
(Research student)

Dr. A. S. Varale
(Research Guide)